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Original Articles

by

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FACTORS COMMON TO SURGICAL LESIONS OF THE BILIARY TRACT

ALLEN O. WHIPPLE*

IN introducing the symposium dealing with the treatment of several of the important lesions of the biliary tract it is my duty to call attention to the three factors that determine the pathogenesis of every lesion of the biliary tract requiring surgical therapy. These factors are, first, disturbed metabolism of cholesterol and salts of the bile acids resulting in gallstone formation—this may be named factor M. Secondly is the factor of infection or inflammation, spoken of as I. The third factor is obstruction, or factor O. Singly or in combination one or more of these factors is present in the pathogenesis of every lesion of the biliary tract requiring surgery.

A knowledge of these factors and the location of them in the different parts of the biliary tree is of the greatest help in the diagnosis of the lesions, in determining the indications for therapy, in following the postoperative course of the patient, in treating the complications and in giving the prognosis after operation.

As an example: A patient with a history of repeated attacks of biliary colic without jaundice is seized with severe right upper quadrant

* From the Department of Surgery, Columbia-Presbyterian Medical Center, New York, N. Y.
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pain followed by extreme tenderness over a palpable mass in the region of the gall bladder. Factors M and I can be considered present and limited to the gall bladder. Cholecystectomy is indicated. An acutely inflamed gall bladder containing a single large stone is removed. The patient has a smooth postoperative course without jaundice and with normal bowel movements. The factors M and I have been removed. Factor O was not present.

Another example: A patient, 52 years old, with no history of previous attacks of pain develops a gradually increasing jaundice and acholic stools. A large pear-shaped gall bladder develops in the right upper quadrant. The diagnosis of a carcinoma of the bile duct or ampullar region below the cystic duct with factor O as the single factor in the pathogenesis of the disease is obvious. If at operation the gall bladder only is drained, factor O is still present and the biliary fistula will persist. Thus the prognosis is determined by evaluating factor O.

For the medical student as well as the practitioner a clear understanding of these factors in relation to pathogenesis, diagnosis, operative indications and procedure, postoperative course and late prognosis in biliary tract disease requiring surgery is essential. Attention to these factors and their location in the biliary tree makes the study of bile tract disease interesting, the therapy sound and the prognosis accurate.

THE SURGICAL TREATMENT OF ACUTE CHOLECYSTITIS*

Introductory Remarks

GEORGE J. HEUER

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IT WAS, I think, in 1910 or 1911 that a private patient of Dr. Halsted was admitted to the Johns Hopkins Hospital with the symptoms and signs of acute cholecystitis. I saw the patient with Dr. Halsted. He decided to operate; and so as soon as the patient was properly prepared she was taken to the operating room. I assisted Dr. Halsted at the operation.

The gall bladder was large and acutely inflamed and the omentum was loosely adherent to it. Without hesitation and without comment to indicate that he was doing something unusual he proceeded to do a cholecystectomy. It was the first cholecystectomy I had seen for acute cholecystitis. I was struck by the smooth convalescence of the patient and the case made a great impression upon me.

At the time, cholecystostomy with drainage was practically the universal treatment for gall stone disease of the gall bladder; and the deliberate attack upon the gall bladder in the acute phase of acute cholecystitis was rare indeed. When in 1922 I went to Cincinnati, I found again that operation for acute cholecystitis was not practiced, the acute process being allowed to subside; and if and when it did subside, cholecystostomy was commonly done although cholecystectomy was being discussed and practiced.

I had a good opportunity in Cincinnati to observe the course of acute cholecystitis under a waiting policy. I have to admit that I observed the gall bladder perforate while the patient was in the hospital, and that I saw not only extracholecystic localized abscess but generalized peritonitis supervene. I also observed that the gall bladder in acute

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cholecystitis may proceed in its pathological course to gangrene and perforation in the presence of subsiding and minimal signs and symptoms. Such observations led me to operate more frequently and to encourage my resident staff to operate in the acute phase of the disease; and before I left Cincinnati to come to New York I had decided that early operation in acute cholecystitis was the surgical treatment of choice.

Early operation in this disease was then established by me as a policy to be followed by my staff on my ward service at the New York Hospital, and it has consistently been followed since September, 1932. Dr. Glenn will tell you the results of such a consistent policy.

THE SURGICAL TREATMENT OF ACUTE CHOLECYSTITIS

FRANK GLENN

Associate Professor of Clinical Surgery, Cornell Medical College

Over a period of thirteen years, from September 1, 1932, to September 1, 1945, a total of 527 patients with acute cholecystitis were operated upon in the New York Hospital. There were thirteen deaths—a mortality rate of 2.46 per cent. It is the purpose of this discussion to present our definition of the surgical treatment for cholecystitis and to elaborate in some detail the operative procedures that are commonly employed. In the discussion of these operations the indications and contraindications for each procedure are reviewed and the resulting complications discussed.

By the surgical treatment of acute cholecystitis we mean operating upon the patient when adequately prepared unless there is some contraindication that is not immediately reparable. The gall bladder has been removed in 460 patients, or 87.4 per cent of those subjected to operation, and cholecystostomy was performed in sixty-seven cases, or 12.6 per

cent. The additional procedure of exploration of the common duct has been limited to those in which indications were definite, and these totalled 47, or 8.9 per cent. The policy has been adhered to that the welfare of the patient is continually kept in mind and that the operative procedure employed has been one of the greatest possible benefit and least hazard. The operation is not decided upon entirely before the procedure is undertaken. For instance, if during operation a cholecystostomy seems to be the procedure of choice, a cholecystectomy is abandoned.

ACUTE CHOLECYSTITIS—NEW YORK HOSPITAL
September 1, 1932, to September 1, 1945

Total cases	527
Deaths	13
Mortality	2.46%
Operative Procedures	
Cholecystectomy	460
Cholecystostomy	67
	(12.6% of total operations)
Common Duct Exploration	43

Cholecystostomy was performed in 67 instances and was followed by 5 deaths. This procedure is clearly indicated under certain circumstances, as when the patient is too ill to withstand cholecystectomy or when cholecystectomy presents too great difficulties. For the extremely debilitated patient or for the very ill, we doubt if there are any contraindications for cholecystostomy because it may be done under local anesthesia, disturbing the patient very little, and at the same time the simple procedure may be a life-saving one. The decompression of the biliary tract averts catastrophe by preventing progressive liver damage if complete biliary obstruction is present.

In determining the type of operation to be done, the gross appearance of the presenting pathological changes is of importance. In the first place, if there is gangrene and perforation with accompanying generalized peritonitis, simple drainage of the abdomen together with cholecystostomy is indicated. If there is gangrene and perforation which has resulted in localized peritonitis or abscess in the region of the extrahepatic portion of the gall bladder, then one may choose between cholecystectomy and cholecystostomy. However, in the presence of ex-

tensive adhesions of omentum to the gall bladder and into the biliary fossa, it is indeed questionable whether these should be disturbed and a cholecystectomy done. If the patient is unusually ill and if postoperative complications appear in the offing, then certainly cholecystectomy should not be attempted. Perforation of the gall bladder with a small abscess or perforation into the adjacent liver tissue is no contraindication to cholecystectomy. The patients with simple acute cholecystitis are in general best treated by cholecystectomy.

Common duct exploration in acute cholecystitis has been limited in our clinic to those patients with unequivocal indication of common duct obstruction. If this exists, common duct exploration should be undertaken even though it adds additional risk to the procedure. The incidence of postoperative complications is in this series apparently increased. At the same time it may be said that these patients are usually in the group that is more seriously ill. For the extremely ill, jaundiced patient, decompression (that is, cholecystostomy) may be utilized as a compromise procedure, having in mind, of course, following the subsidence of jaundice, the exploration of the common duct with the patient in a greatly improved condition.

The presence of jaundice requires the determination of blood prothrombin and the evaluation of any bleeding tendency, and in the presence of acute disease time may not be afforded for this. For such patients the use of whole blood transfusions and parenteral administration of Vitamin K may prevent serious postoperative hemorrhage.

The common duct was explored in 47 of these patients, an incidence of 8.9 per cent. Stones were recovered in 29 of these, or 61.7 per cent. It is probable that the opening of the common duct in the patient without stones does not materially increase the postoperative complications. On the other hand, failure to remove common duct stones may lead to catastrophe. Therefore, when the surgeon is unable to conclude definitely whether or not there are stones, it may be better judgment to open the common duct.

The operation of choice in acute cholecystitis is cholecystectomy. The removal of the gall bladder interrupts the pathological process and averts the danger of gangrene and perforation. This procedure is sometimes contraindicated because of (1) the presence of peritonitis due to perforation of the gall bladder. In this situation an extensive operation is contraindicated because of the gravity of the patient's condition.

(2) Conditions which make it difficult to identify the important structures in the biliary fossa. When the gall bladder is greatly distended and adherent, the adjacent viscera may be so distorted that anatomic relationships are obscured. In this situation there is danger of inadvertently injuring the hepatic vessels or the common duct. (3) The presence of a severe jaundice caused by obstruction in the common duct is a contraindication to an extensive operative procedure. It is usually better to drain the gall bladder and thereby relieve the jaundice than to subject the patient to removal of the stone from the common duct. (4) In a patient whose general condition is so grave that a general anesthetic and prolonged operation are not justified. This state of affairs is likely to arise when the cholecystitis is superimposed upon systemic disorders, such as hypertension or cardiovascular and renal disease. In such cases a compromise must be sought in the form of surgical treatment which, without adding to his burden, tides the patient over the immediate crises.

ACUTE CHOLECYSTITIS—NEW YORK HOSPITAL
September 1, 1932, to September 1, 1945
Patients Fifty Years of Age or Over

Total	175
Deaths	9
Mortality	5.14%

Operative Procedures

Cholecystectomy	140
Cholecystostomy	35
	(20% of total operations)
Common Duct Exploration	22

In the series of 527 patients treated surgically, 175 were fifty years of age or over. There were nine deaths, or a mortality rate of 5.14 per cent. One hundred forty were subjected to cholecystectomy. Thirty-five, or 20 per cent of the 175, were treated by cholecystostomy. Twenty-two had in addition to these operations exploration of the common duct. The mortality rate of 5.14 per cent of these patients who were fifty years of age and over indicates the definitely greater risk associated with them than those of less than fifty years of age with a mortality rate of 1.13 per cent. The following chart with an analysis of the nine deaths demonstrates the complications that terminated fatally.

In the consideration of this group of deaths it may be of significance

SUMMARY OF DEATHS AFTER OPERATION

	Sex	*Age*	*History of Biliary Disease In Years*	*Duration of Attack*	*Jaundice*	*Findings*	*Operation*	*Cause of Death*
1.	F	66	8 plus	3 days	+	Acute cholecystitis with perforation, peritonitis	Cholecystectomy with drainage	Peritonitis
2.	F	67	4 plus	7 days	0	Acute cholecystitis with gangrene	Cholecystostomy	Peritonitis, bacteremia
3.	F	50	20 plus	10 days	+	Acute cholecystitis, cholelithiasis, common duct obstruction	Cholecystostomy	Bacteremia, stone in common duct, thrombosis hepatic artery
4.	M	72	7 plus	8 days	+	Acute cholecystitis, cholelithiasis	Cholecystostomy	Hepatic failure, biliary cirrhosis
5.	F	57	Inadequate history	4 days	0	Acute cholecystitis, cholelithiasis	Cholecystectomy, drainage abscess	Subhepatic abscess*
6.	F	70	12 plus	8 hours	0	Acute cholecystitis, cholelithiasis	Cholecystectomy	Coronary occlusion, cardiac failure
7.	F	64	2 plus	2 days	+	Acute cholecystitis	Cholecystectomy with drainage	Adrenal insufficiency
8.	F	54	4 plus	3 days	+	Acute cholecystitis, common duct obstruction	Cholecystectomy, common duct exploration	Leakage from cystic duct, subphrenic abscess, pancreatic necrosis
9.	F	72	?	3 days	0	Acute cholecystitis, carcinoma of cecum	Cholecystectomy, ileocolostomy	Intestinal obstruction, hypertensive cardiac disease

* No autopsy.

that all but one were women and the duration of known biliary tract disease was of long standing—longer, I feel, than the histories recorded. Furthermore, the duration of the immediate attack was of two days or more with one exception. Jaundice was marked in five of the patients.

In patients fifty years of age and over acute cholecystitis is a more serious disease than in the younger age group. The mortality rate is almost five times as great in this series. It has been our experience that changes in the vascular system, i.e., arteriosclerosis, hypertension, and diabetes, are greater in those who have biliary tract disease than in a corresponding number without it. Cowdry in a volume on arteriosclerosis places the incidence of arteriosclerosis in the general population at 25.6 per cent for those between fifty and sixty, and 38 per cent for those over sixty. McCallum found that patients over fifty dying as a result of biliary tract disease associated with gall stones showed an incidence of arteriosclerosis of 68 per cent. The trend of our population toward the older age groups indicates that we may anticipate an increasing number of these geriatrical problems unless they can be reduced by preventive surgery. For biliary tract disease it means operating in the earlier decades when acute cholecystitis represents an early phase of the disease. If our contention is correct, a deleterious effect upon the vascular system may be interrupted.

ACUTE CHOLECYSTITIS—NEW YORK HOSPITAL

September 1, 1932, to September 1, 1945

Patients Under Fifty Years of Age

Total	352
Deaths	4
Mortality	1.13%

Operative Procedures

Cholecystectomy	320
Cholecystostomy	32
	(9% of total operations)
Common Duct Exploration	25

The remaining 352 of the 527 patients were under fifty years of age. There were four deaths, a mortality rate of 1.13 per cent; 320, or 90 per cent, were subjected to cholecystectomy, and 32, or 9.1 per cent were treated by cholecystostomy. Only twenty-five, or 7.1 per cent, had in addition to one of the above procedures exploration of the common duct. This is a far more favorable outcome than our experience with the group of patients who were fifty years and over.

SUMMARY OF DEATHS AFTER OPERATION
UNDER 50 YEARS

	Sex	*Age*	*History of Biliary Disease In Years*	*Duration of Attack*	*Jaundice*	*Findings*	*Operation*	*Cause of Death*
1.	M	41	5 years	1 day	+	Acute cholecystitis	Cholecystectomy	Cardiac and renal failure, liver death
2.	F	49	15 years	3 days	+	Acute cholecystitis	Cholecystectomy	Subdiaphragmatic abscess, peritonitis
3.	F	49	12 years	2 days	0	Acute cholecystitis, stones in common duct, acute pancreatitis	Cholecystectomy, choledochotomy	Pulmonary emboli 27th p.o. day*
4.	M	44	4 years	10 days	0	Acute cholecystitis	Cholecystectomy	Hypertension, cardio-renal failure

* No autopsy.

The chart (page 290) of the four deaths is self-explanatory and emphasizes in each instance that the biliary disease was of long standing. This suggests that acute cholecystitis is but a phase of the disease.

Given a patient with a definitely established diagnosis of acute cholecystitis, our policy provides for his or her surgical treatment as soon as adequate preoperative preparation has been carried out. There is no undue haste, no neglect of this preparation, and never is it to be undertaken where operation of any kind is contraindicated. It may require several hours to prepare these patients; no step should be neglected. A surgical operation on the biliary tract is to each patient a serious procedure, never to be entered into lightly, and those with acute cholecystitis are certainly no exception. Once prepared, the operation should be undertaken and the nature of that procedure and the extent determined by the findings and the general condition of the patient.

How different is this from the so-called conservative attack which considers these patients a medical problem, leaves them in their homes where complications may develop and be unrecognized. There can be little disagreement that in a well regulated hospital the constant observation and care of a patient will be far more efficient than in the home, where the patient may be seen once a day by the physician. I need not remind you that laboratory data, temperature records, and personal observation by more than one individual are of great value in determining the course of events in any pathological process.

It is the duty of the surgeons to present this to the general practitioner and to demonstrate that such a policy will diminish the deaths due to this particular entity if and when they are considered surgical subjects and are admitted to the hospital.

I feel that in the heat of argument there have been radical claims made by those who favor early operation and those who are opposed to it. Those in favor often insist that operation be done within a period of hours without dwelling long on preoperative preparation, and this certainly is not sound. On the other hand, those opposed to operation assume the policy that surgery is not indicated and that it should not be carried out, and they cite figures based not upon the early surgical treatment of acute cholecystitis but upon the treatment of the complications that arise from these cases.

In conclusion, it should be reiterated that successful surgery is dependent upon every detail associated with it, and the patient with acute cholecystitis is no exception. Pre- and postoperative care and meticulous surgery are necessary to support the policy that we maintain.

TREATMENT OF CHRONIC CHOLECYSTITIS, WITH AND WITHOUT STONE: INDICATIONS AND CONTRA-INDICATIONS FOR CHOLEDOCHOSTOMY*

FREDERIC W. BANCROFT

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Two subjects have been assigned to me: namely, chronic cholecystitis and indications and contraindications for choledochostomy.

In the limited time assigned to me, it would be foolish for me to attempt to cover the problem of cholecystitis with stones. This, I believe, is not the problem that bothers the clinical surgeon the most. The clinical surgeon is perturbed by a patient who comes complaining of right upper quadrant pain, moderate flatulence, some tenderness over the gall-bladder and a cholecystogram that does not show presence of calculi. The cholecystogram may or may not show a non-functioning gall-bladder.

At the time of operation, a gall-bladder may be found with moderate thickening of the wall and the presence of some adhesions about the ampulla or fundus, or no adhesions. There may be areas of subperitoneal fat deposits as described by Deaver and Willy Meyer. No stones can be palpated in the gall-bladder. This pathological condition has been aptly described by Evarts Graham as minimum cholecystitis. It is this particular phase of gall-bladder surgery upon which I wish to concentrate. Evarts Graham has described 4 types of chronic cholecystitis without stone. These are, namely, and I quote him:

"The term minimal lesion was assigned to those cases in which the gall-bladder wall was not greatly thickened, the organ contained concentrated bile and on microscopic examination there were a few lymphocytes in the wall.

"A diagnosis of cholesterosis was made when the mucosa of the gall-bladder contained the yellowish plaques that are characteristic of lipoid deposits.

* Presented February 1, 1946 before the Section of Surgery, The New York Academy of Medicine, in the Symposium on Surgery of the Gallbladder.

"Chronic catarrhal cholecystitis was said to be present when there was edema of the mucosa, a greater infiltration of lymphocytes than in the minimal lesion and some muscular thickening.

"Chronic fibrous cholecystitis was the term applied to those gall-bladders with markedly thickened walls, cuboidal epithelium that often is absent in places, and diverticular crypts. This type of lesion is almost always accompanied by biliary calculi."

The etiology of chronic cholecystitis without stones is still a disputed problem. There are four main possible etiological causes, no one of which describes all of the pathological findings of chronic cholecystitis. These are, namely:

1. *Infection*: The infection theory arises from the fact that infection may be carried to the gall-bladder through the common duct or through the lymphatics.

Sappey has shown that "a considerably large number of fairly large lymph vessels pass along the inferior surface of the liver over the body of the gall-bladder from the adjoining quadrate lobe and the right lobe, to form an extensive anastomosing network of vessels in the neighborhood of the neck of the gall-bladder. Others, derived from the same sources, pass behind the gall-bladder to terminate in the same region. There are apparently numerous anastomosing lymph capillaries between the lymphatics of the liver and the gall-bladder."

Sudler and Evarts Graham have offered the hypothesis of the hemato-lymphatic route. Bacteria injected into the portal vein have been shown to form focal areas of infection in the liver and bacteria have been found in lymphatics surrounding the gall-bladder.

In 1924 I injected lamp black into the portal vein and found it on microscopic examination 48 hours later in the lymphatics surrounding the gall-bladder.

There are four possible concepts of infection of the gall-bladder:

1. Descending infection of the liver by bacteria carried down in the bile and ascending into the cystic ducts.

2. Ascending infection from the duodenum up the common bile duct and thence into the lumen of the gall-bladder.

3. Hematogenous infection of the gall-bladder and its bile ducts, and

4. A spreading infection to the wall of the gall-bladder through the lymphatics arising in the liver.

Fig. 1.—Normal gall-bladder removed at autopsy of traumatic case shortly after death. Thin stroma, narrow elongated villi; no round cells in muscularis.

It has been noted by many surgeons that chronic cholecystitis is often a sequel of suppurative lesions in the lower abdomen. In 1924, I published an analysis of thirty-eight consecutive cases of minimum cholecystitis without stone. In this particular series, eleven women and five men had had previous operations for inflammatory lesions of the lower abdominal organs. In opposition to the infectious theory is the fact that bacterial studies of the bile removed in most cases proved the bile to be sterile even in acute cholecystitis. Judd and his associates found a positive culture in the bile in only 14 per cent of the cases of cholecystitis and positive culture in the gall-bladder wall in 49 per cent.

2. *Cholesterosis of the gall-bladder, the so-called "strawberry gall-bladder."* This is a definite pathological entity which is grossly shown on observing the mucosa of the gall-bladder. It is non-infectious in

Fig. 2.—Chronic cholecystitis, seven years duration. Gall-bladder adherent to duodenum. Contained black bile on aspiration. Granular fat seen on cystic duct. Numerous round cells in muscularis and submucosa. Cholecystectomy. Patient well.

character as far as I know, and is due to a chemical change in the bile. Cholesterol is deposited in the tips of the papillae causing thickening of the papillae and often associated with a round cell infiltration of the submucosa. Experimental studies show that even with this cholesterosis, the concentration of the bile by absorption through the gall-bladder wall is not greatly delayed.

3. *Reflux pancreatic ferments through the cystic duct into the gall-bladder.* Colp and Doubilet have shown that if there is an anomaly of the common duct so that the pancreatic duct enters into the common duct before it reaches the papilla of Vater in cases of spasm of the sphincter of Oddi, there may be a reflux passage of pancreatic juice associated with bile into the gall-bladder. Wolfer showed in experi-

Fig. 3.—Duration five years. Edema of villi. Thickening of muscularis with round cell infiltration. Cholecystectomy. Poor result.

ments with animals that where the pancreatic duct enters the common duct some distance proximal to the sphincter of Oddi, if he created a partial obstruction of the common duct between the entrance of the pancreatic duct and the sphincter of Oddi, a type of chronic cholecystitis with ulceration of the mucosa results due to pancreatic reflux.

4. *Partial obstruction of the cystic duct.* Warren Cole has demonstrated that if a partial stricture of the cystic duct be created experimentally in animals, there is a concentration of bile double its normal content in the gall-bladder. He has been able to show that a type of chronic cholecystitis results.

We may readily assume from the summary of these various causes that we are not in common accord as to the pathology or etiology of chronic cholecystitis without stones.

Fig. 4.—Duration four months, strawberry gall-bladder. Moderate round cell infiltration. Some thickening of villi. Lipoid deposit shown with special stain. Cholecystectomy. Good result.

In 1924, I summarized the histories, physicals, operative findings, microscopic and pathological findings and the follow-ups on thirty-eight consecutive operative cases on Dr. Pool's service at the New York Hospital. I was perturbed then, as I am now, in diagnosing and operating upon cases of minimal cholecystitis without stone. At that time we had most of the diagnostic measures that we have now, with the exception of the cholecystogram, and I am not at all convinced that the cholecystogram has added much to our diagnostic acumen, even in cases of non-filling of the gall-bladder. Evarts Graham, in a diagnosis of similar cases, felt that it was of no diagnostic significance in this type of case.

Incidence: There were twenty-four women, or 63.2 per cent, with an average age of thirty-six at the time of operation; fourteen men,

TABLE I—IMPORTANCE OF PATHOLOGIC CHANGES TO PROGNOSIS AFTER CHOLECYSTECTOMY*

	Well	*Improved*	*Unimproved*	*Postoperative Deaths*	*Total*
Minimal lesion	11	22	21	3	57
Cholesterosis	14	2	14	1	31
Chronic catarrhal cholecystitis	18	16	13	4	51
Chronic fibrous cholecystitis	2	3	0	0	5
Cholesterosis with stone	6	11	0	0	17
	51, or 31.7%	54, or 33.5%			161

or 36.8 per cent with a similar average age at the time of operation. The average duration of symptoms I analyzed was 2½ years.

History Analysis: The chief complaint in this series was pain and soreness in the epigastrium or right upper quadrant. The pain radiated to the back in twenty-four, or 63.2 per cent of the cases. In nine of the cases it was described as dull and in twenty-nine as knife-like. Thirteen complained of indigestion and gas after eating, symptoms which had persisted over a considerable period of time. There was vomiting during the attacks in nineteen cases, or 50 per cent. Eleven women and five men had had previous operations for inflammatory conditions of the lower abdominal organs. In addition, five women and seven men had definitely diseased appendices removed at operation. This made the total number of patients with inflammatory conditions of the lower abdomen, twenty-nine, or 73.7 per cent.

Physical Examination: Physical examination usually revealed patients with a moderate amount of adiposity. Usually they did not appear particularly ill. Rigidity was shown in a moderate degree in nine cases; marked in four, and absent in twenty-five. Tenderness in the right upper quadrant at Murphy's point on deep pressure was noted in thirty-five cases and absent in three. The ante-operative diagnosis was cholelithiasis thirteen times; cholecystitis fifteen times; adhesions about the duodenum four times; and ulcer of the duodenum two times. In four the ante-operative diagnosis was not mentioned.

Operative Procedure: Cholecystectomy was performed thirty-one times; cholecystostomy was performed six times; and inversion of a

TABLE II—CHOLECYSTOGRAM AND PROGNOSIS: 114 CASES*

Type of Cholecystographic Response	*Total*	*Clinical Results*				*Percentage*
		Well	*Improved*	*Unimproved*	*Postoperative Deaths*	*Well or Improved*
Normal gallbladder	10	5	1	4	0	60
Deformed shadow	8	4	2	2	0	75
Faint shadow	75	22	22	28	3	59
No shadow	21	6	7	5	3	62
	114	37	32	39	6	60

* Note: Tables I and II were found in "A Consideration of the Stoneless Gallbladder" by Evarts Graham, M.D., and W. Arthur Mackey, *J.A.M.A.* Nov. 17, 1934.

distal portion of the gall-bladder in hour-glass constriction, once.

The appendix was removed in twenty cases and was found to be definitely diseased in twelve of the twenty as noted by the operator. Only definitely marked lesions of the appendix have been classed in this series as diseased.

Follow-Up: Thirty-seven of the thirty-eight cases were examined and personally seen in the Follow-Up Clinic, for periods varying from six to thirty-nine months. There was no operative death in this series. There were three subsequent operations, one a case which came back for incision and drainage of an abdominal wound abscess three weeks after leaving the hospital. One case developed incisional hernia, and at a subsequent operation this was repaired. One case, cholecystostomy, came back complaining of pain. An operation was done, but the adhesions were so dense that no satisfactory operative procedure could be carried out.

Thirty cases were classified as good, and seven classed as poor, making a total of 81.5 per cent good results. Subdividing the series into operations, there were: thirty-one cholecystectomies with twenty-seven good results and four poor results, or a percentage of 88.5 good results. There were six cholecystostomies with three good results and three poor results, making a total of 50 per cent with good results.

The case was classed as poor when abdominal pain and indigestion of varying degree still persisted. Five patients complained of indigestion and gas after eating. Eight patients complained of some upper abdominal pain. No history of vomiting was obtained in any of the post-

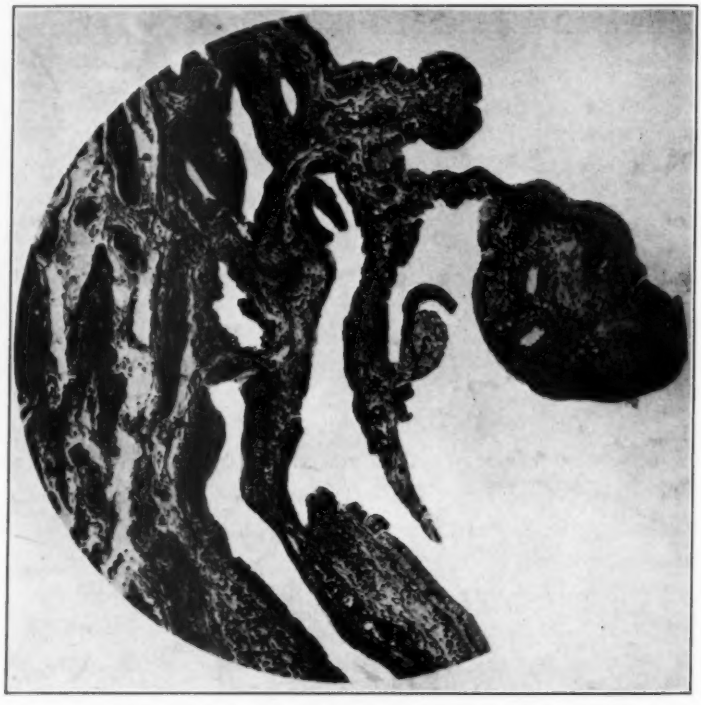

Fig. 5.—Eight years duration. Gall-bladder found thickened at operation. No adhesions. Mucous membrane appeared slightly reddened. Knob-like villi with some ulceration of mucous membrane. Round cell infiltration. Cholecystectomy. Good results.

operative cases. Eight patients still complained of constipation.

Graham has noted, as have others, that it is difficult to obtain a microscopic study of a normal gall-bladder as a comparison. Also there must be involuntary changes throughout the years that create certain moderate changes in the gall-bladder that correspond with similar changes in the appendix. The difficulty in obtaining a normal gall-bladder specimen for microscopic examination comes from the fact that these must be obtained from autopsies. An autopsy is not usually performed immediately after death and autolysis takes place within the gall-bladder. Douglas Symmers was good enough to obtain for me the gall-bladder of a young man who had been killed in an accident. The gall-bladder was opened and imbedded in formalin within two hours

Fig. 6.—Strawberry gall-bladder, one year duration. Thickened knob-like villi with edema and ulceration of the tips. Cholecystectomy. Good result.

after the patient had been killed. This specimen is the only normal gall-bladder that I have been able to find in the literature and I wish to show it with some of the photomicrographs of pathological specimens.

There seem to me to be three different types of inflammatory lesions noted in the gall-bladder.

1. Cholesterosis of the gall-bladder with thickened tips of papillae and deposits of cholesterol through the mucosa.

2. Bulbous, edematous papillae, often with ulcerations of the mucosa and round cell infiltration of the submucosa.

3. Thickening of the subserosal layers of the gall-bladder with dilated lymphatics often containing groups of polynuclear leukocytes with a round cell infiltration in the muscularis.

Fig. 7.—Duration, one and one-half years. Stain for lipoid deposit shows knob-like villi with lipoid deposit in mucosa and submucosa. Cholecystectomy. Good result.

This latter group I assume to be due to extension of infection from the liver through the lymphatics anastomosing over the gall-bladder.

I must confess that our result of 88.5 per cent good results is either due to the fact that we were very conservative on the cases operated on, as the average duration of symptoms was over 2½ years, or our series was too small. Four to five successive bad results would markedly change these figures, which are much better than the general results published. For instance, Evarts Graham states as follows:

"The ultimate results in those cases in which no stones were present showed only 60 per cent of the patients considered themselves well. There was an equal number of gall-bladders which had a few adhesions as had many adhesions. In the class listed as greatly improved, nearly three times as many patients showed only a few adhesions

Fig. 8.—Numerous round cells seen in submucosa and muscularis. Cholecystectomy. Good result.

around the gall-bladder. On the other hand, all of the seventeen patients with cholesterosis and stone showed either marked improvement or complete recovery from the symptoms.

"Of the stoneless cases only 33 per cent gave a history of biliary colic but 76 per cent of these patients consider themselves well or improved. On the other hand, only 58 per cent of those without biliary colic were well or improved."

Summary

We must be extremely cautious in operating on patients when there is no evidence of biliary calculi. The Meltzer-Lyon test may aid us if we receive no help from cholecystograms. The B bile containing bile-stained bacteria or leukocytes is suggestive of a chronic cholecystitis.

TABLE III—MINIMUM CHOLECYSTITIS WITHOUT STONE

	Good	*Poor*		*Percentage of Cures*
31 Cholecystectomies	27	4	=	88.5
6 Cholecystostomies	3	3	=	50

It is unfortunate that one cannot open the wall of the gall-bladder, inspect its mucosa and then re-suture it. This procedure has proved disastrous in some hands. It is my opinion that if the patient has had right upper quadrant symptoms of pain with colic not as severe as colic due to calculus, which is persistent for at least two years, and if there is definite localized tenderness, we are justified in exploring. If the gall-bladder shows moderate thickening of the wall and poor emptying by compression, cholecystectomy is justified, although we must admit at that time that we will have a certain percentage of failures as far as curing the patient is concerned.

Indications and Counter Indications for Common Duct Drainage. History: If the patient has had a definite history of antecedent jaundice, the operator must convince himself that there is no obstruction in the common duct. Repeated attacks of severe vomiting with pain in the right lower dorsal region of the back is also suggestive of calculi in the duct. When the patient is operated upon, one must of course palpate the common duct. This method however offers numerous failures, as often surgeons have not felt any stone in the duct and on opening the duct have found calculi.

The gall-bladder containing numerous small stones, a thickened head of the pancreas, or a dilated common duct, is an object of suspicion. It is my impression however that we have gone too far to the left in our exploration of the common duct. For instance, Arthur Allen states that in his own personal series of 266 biliary tract operations, 159 cases, or 59.7 per cent of the total series had duct explorations, in whom stones were found in ninety-eight instances, i.e., 61.6 per cent of ducts explored revealed calculi; or a negative finding in 38.4 per cent, who were explored without finding calculi.

Frank Lahey, in discussing Allen's paper, stated that stones can be found in 18 to 20 per cent. In 4 per cent of Lahey's cases stones were not present in the gall-bladder and were present in the common

duct. In 39 per cent of Lahey's cases where calculi were found in the common duct, jaundice was not present and never had been present.

In analyzing my own cases, I find that I have explored the common duct and found calculi in 17 per cent of cholecystectomies and I have not found calculi in 10 per cent.

I find, however, that my fear of leaving calculi is making me explore more ducts than I think should be explored. The difficult problem I have encountered is whether or not a common duct is dilated and if it is dilated, is it due to the occlusion of the cystic duct with compensatory dilation of the common duct, or is it due to distal obstruction? There is no question that one increases the morbidity and mortality by unnecessary common duct drainage and I am coming to the conclusion that if the common bile duct, although dilated, does not appear thickened or inflamed, one is relatively safe unless there are other definite indications for incising the duct.

Barney Brooks states that he never puts a tube in the common duct; that he closes it and drains to Morrison's space. So far, I have not had the courage to follow this procedure but I believe that it may have definite merit. It certainly saves the trauma of pulling any tube out of the duct when one wishes to discontinue common duct drainage.

Aspiration of the common duct by needle puncture is an aid in determining if there be stones in the duct. Clear bile without flakes of fibrin in it is a fairly good indication that no stone is present. However a word of caution should be offered about needle aspiration. Even with a fine needle inserted into the duct, bile is apt to leak from the puncture hole for a considerable period of time and drainage of Morrison's space must be established in cases where this has been done if the duct is not opened. If the duct is opened immediately, cholangiograms taken on the operative table are a safeguard to assure the complete removal of calculi. If an operating room is properly equipped, it should not lengthen the operative time to any great degree and may save the patient a secondary operative procedure.

Conclusions

The tragedy of inflammatory common duct lesions from cholecystectomy will be adequately described by Dr. Colp but I feel that we must stress the importance of a primary atraumatic cholecystectomy, and insofar as possible, a protection of the common duct in our operative procedure. I have found no method of common duct drainage that seems to me harmless if a large series is analyzed.

THE REPAIR OF STRICTURES OF THE COMMON AND HEPATIC BILE DUCTS*†

RALPH COLP

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THE most frequent cause of benign stricture of the hepatic and common bile ducts is the ultimate result of a direct injury to these important structures during the course of a cholecystectomy. Inadequate exposure, hemorrhage and anatomic abnormalities may result in the inadvertent ligation, clamping, or excision of part of the hepatic or choledochus during the removal of the gallbladder. The accident is not often recognized at the primary operation and only the subsequent course of events and operative findings may reveal the traumatic nature of the pathology. But operative injury alone cannot account for the complete absence of most of the common bile duct in some patients. Whipple[1] discussed three instances of irreparable stricture of the choledochus in which he felt sure that the common bile duct had not been injured at the time of cholecystectomy. When these patients had become deeply jaundiced, requiring a second operation, nothing was found but a shred of dense connective tissue extending from the duodenum to the portal fissure. He felt that such an extensive destruction of the common bile duct could only be due to the necrotizing effect of an activated pancreatic reflux. It is barely possible that the cases of chronic choledochitis described by the French surgeons in which the common bile duct resembles a pipe stem and into which a fine probe could not be introduced may be caused by repeated pancreatic reflux rather than by biliary stagnation and subsequent cholangitis. There are other cases in which merely the terminal portion of the common bile duct is strictured, the narrowing being due either to a chronic pancreatitis or to a stenosis of the papilla of Vater secondary to local ulceration.

Secondary operations upon the extra-hepatic bile ducts in general, and plastic procedures in particular, are often complicated and involved problems. They may be very time consuming and productive of shock.

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† Read before the Surgical Section, The New York Academy of Medicine, February 1, 1946.

These patients require adequate and careful preoperative preparation. Surgical exploration is best performed under continuous spinal anesthesia which produces excellent muscular relaxation and renders adequate exposure. During operation a continuous infusion of 5 per cent glucose in normal saline is administered to which blood and plasma may be added. The operative findings in these cases follow a general pattern. The intra-abdominal adhesions are usually firm and dense, and at times the line of demarcation between adjacent viscera appears almost indiscernible, and only sharp knife dissection will delineate their boundaries. The liver, invariably enlarged and occasionally cirrhotic, and the omentum, are usually bound to the peritoneal surface of the anterior abdominal wall and the colon is firmly plastered to the site of the gallbladder bed. When the colon has been separated from the liver, and after the duodenum has been similarly freed, the pathology in the gastrohepatic omentum may be revealed. Occasionally the foramen of Winslow is obliterated so that the familiar anatomic landmarks are extremely difficult to identify. But if the stricture is near the termination of the common bile duct, the dilated choledochus is easily visible. If the scar is in the mid portion of the common duct, a partial narrowing may be seen with a definite enlargement of the proximal canal. However, in most of the cases, only dense scar tissue is found in the region of the hepaticus. This area, bearing in mind the close proximity of the portal vein and hepatic artery should be explored first with a fine hypodermic needle for the aspiration of bile or mucus in the syringe indicates the location of the duct. An incision is then made along the needle as a guide and the surrounding scar is carefully excised, usually exposing a shortened and dilated hepatic duct. In one of our cases the operation had to be discontinued at this point because the general condition of the patient became so precarious that further surgery was deemed inadvisable. The hepatic ducts were simply drained, leaving the restoration of biliary intestinal continuity for a later date. In patients suffering from prolonged biliary obstruction with severe hepatic damage, a two stage operation may be the procedure of choice. Attempts in most of these cases to isolate the distal portion of the common bile duct in the gastrohepatic omentum are futile, for even if it were found, the defect between the choledochus and the hepaticus and the disparity in their lumens would make any type of hepaticocholedochal reconstruction impractical.

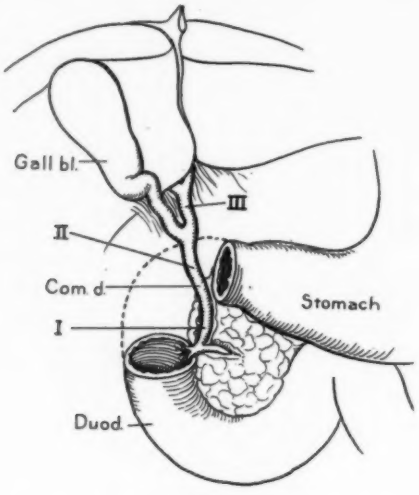

Fig. 1.—A diagnostic representation of the anatomy of the extrahepatic bile ducts.

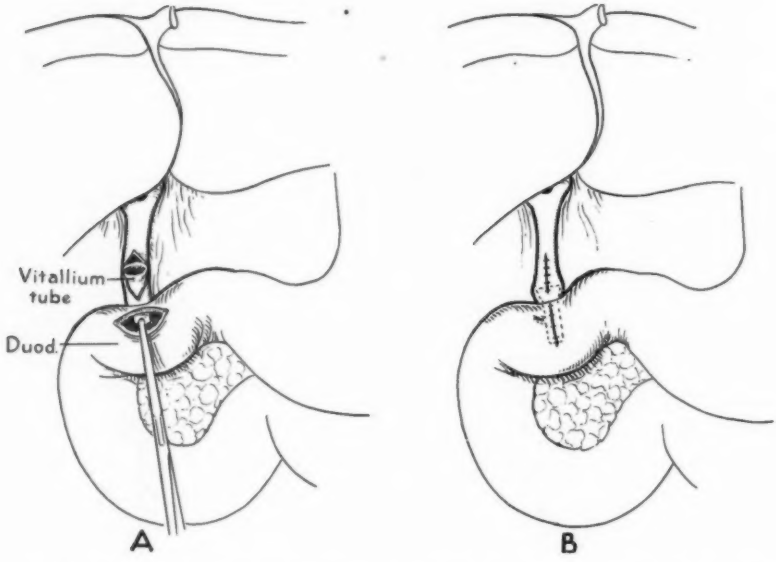

Fig. 2A & B.—Choledochoduodenostomy. A method for the introduction of the vitallium tube for strictures of the papilla of Vater and terminal portion of the common bile duct.

Once the location and the extent of the stricture has been established, a choice of operative procedure may be made, but there are certain cardinal principles which must be observed in any reconstruction of the bile ducts. It was Mayo who first emphasized the importance of uniting mucous membrane to mucous membrane in order to minimize the reformation of scar tissue and it is essential that any anastomosis between the divided duct or between the proximal duct and the intestine must be made without tension and with the maintenance of an adequate blood supply. And finally, if possible, the sphincter mechanism should not be by-passed.

The operative treatment of stricture may be arbitrarily divided into three groups (Fig. 1).

1. *The treatment of stricture of the papilla of Vater and the terminal portion of the common bile duct.*

Occasionally the narrowed sphincter may be dilated by passing graduated sounds through the common bile duct into the duodenum followed if necessary by biliary duodenal intubation. A T or straight tube is inserted via the common bile duct and sphincter into the duodenum. This tube not only provides the delivery of bile into the intestine but its mechanical presence maintains a continual dilatation of the stenotic sphincter area until the T tube is either withdrawn or the straight tube is eventually passed by rectum. If the terminal portion of the duct is compressed by a chronic pancreatitis, the sphincter and the area of stricture may be by-passed by the suture anastomosis of the dilated common bile duct to the adjacent duodenum. Choledochoduodenostomy with or without intubation has been used frequently by many Continental surgeons. While many of the gastroduodenal roentgenograms in these patients demonstrated the presence of barium or air in the common bile duct and its radicles, the incidence of clinical cholangitis was not great. Recently in a case in which a choledochoduodenostomy with intubation was performed for a terminal duct stricture due to a marked pancreatitis, cholangitis occurred within four months, and reoperation disclosed no evidence of the previous anastomosis. The funnel shaped end of a vitallium tube was then introduced into the dilated common bile duct and its other end was drawn into the duodenum, the flange being sutured to the intestinal mucosa. The openings in the common bile duct and in the duodenum were then closed (Fig. 2A & B). The immediate result has been encouraging, but insufficient time has

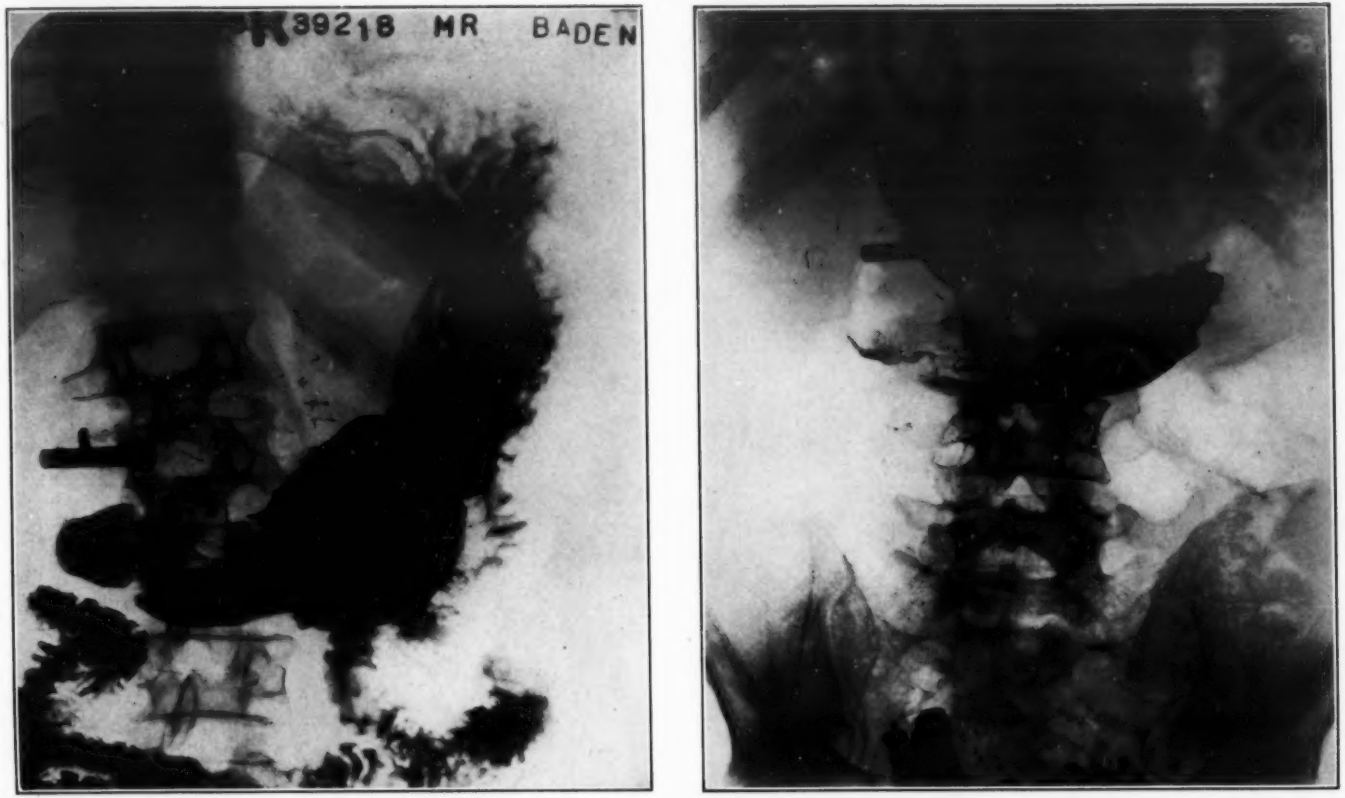

Fig. 3A & B.—A case of chronic pancreatitis with stricture of the terminal common bile duct in which a choledochoduodenostomy was performed with the aid of a vitallium tube. X-rays show the tube in place and the regurgitation of air and barium into the common bile duct and its branches.

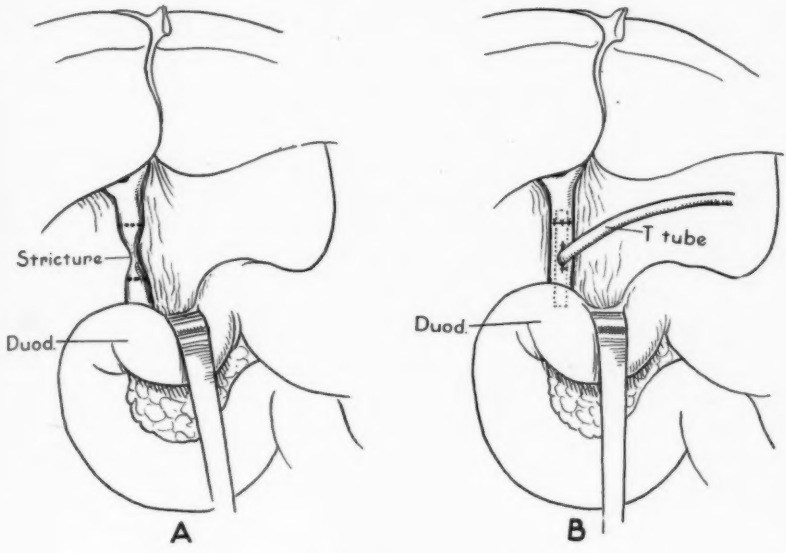

Fig. 4A & B.—A method of reconstruction of the strictured common duct, described by Cattell.

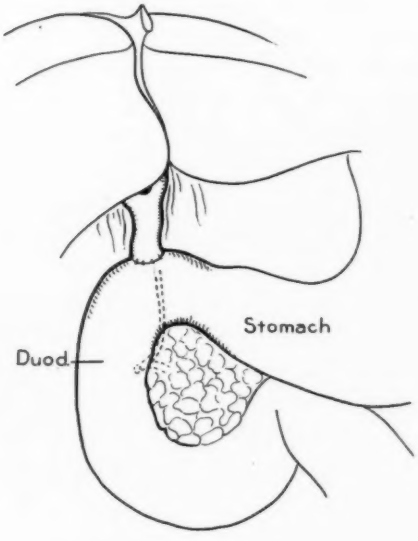

Fig. 5.—Hepaticoduodenostomy.

elapsed to determine the eventual efficacy of this procedure, for while recent roentgenograms reveal the vitallium tube in place, the presence of air and barium in the bile ducts (Fig. 3A & B) denote duodenal regurgitation.

2. *The treatment of stricture of the mid portion of the choledochus.*

In cases in which the extent of the stricture is limited, Cattell[2] recommends that the local area be resected with an end to end suture of the duct and the introduction of a T tube through a normal segment of the choledochus (Fig. 4). The T tube is subsequently withdrawn. Biliary duodenal intubation with either rubber or vitallium for large ductal defects covering the exposed tube with omentum is being used less and less. A careful review of the literature reveals no incontrovertible evidence that this plastic procedure advocated by Sullivan[3] and McArthur[4] ever results in the actual regeneration of hepatic duct epithelium,[5] and while the sphincter mechanism is maintained, the gradual and eventual contraction of the fibrous connective tissue bridge between the reconstructed duct after the tube has been expelled may result in a secondary stricture with stasis and infection. In this type of case, choledochoduodenostomy or choledochojejunostomy seems preferable.

3. *The treatment of stricture of the hepatic duct.*

In those cases in which an appreciable segment of the hepatic duct remains and the distal common duct appears obliterated, the dilated hepatic duct is freed of scar tissue and a direct suture anastomosis of the duct epithelium to the mucous membrane of the duodenum with or without intubation is done (Fig. 5). This procedure requires the minimal amount of operative trauma, and the follow-up results in these cases are not too discouraging. But in those instances in which there has been a complete destruction of the extra-hepatic bile ducts a permanent and adequate fistula must be established between the hepatic duct at the hilus and the intestine by the use of an indwelling tube reinforced by a suture of the serosa of the intestine to Glisson's capsule of the liver. The material used for intubation may be either rubber, vitallium, or tantalum. If rubber is selected, a fenestrated tube of highest quality, radio-opaque if possible and of sufficient tensile strength and calibre so that it will fit snugly into one of the hepatic ducts, is threaded on a heavy probe and introduced upwards into the liver. This tube through its side holes usually drains both ducts effectively. Its distal end, about 8 inches in length, is then passed into an opening made in

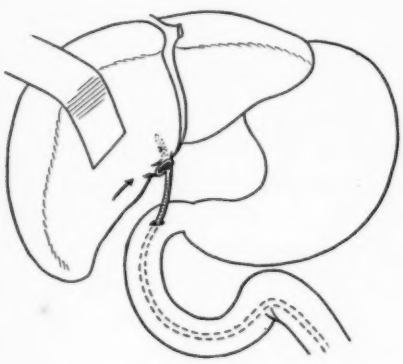

Fig. 6A. — Hepaticoduodenal Intubation. Fenestrated rubber tube inserted into left hepatic duct, and distal end directed through the duodenum toward the jejunum.

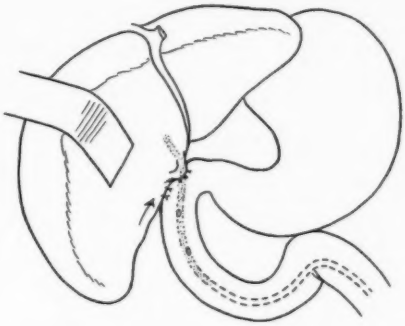

Fig. 6B.—Hepatoduodenostomy. Serosa of duodenum approximated to Glisson's capsule of the liver by interrupted silk sutures.

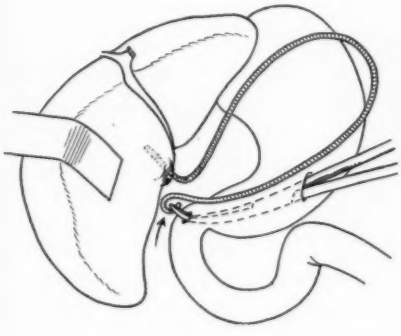

Fig. 7A. — Hepatico-duodeno-gastrostomy. Intrahepatic rubber tube pulled through a duodenotomy into the stomach by a clasp introduced through the pylorus.

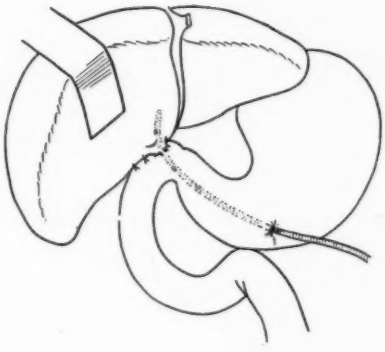

Fig. 7B.—Hepatoduodenostomy. Suture of the duodenum to the liver with interrupted sutures. End of tube made to emerge from stomach similar to a Kader Stamm gastrostomy.

the opposing duodenal wall and directed preferably in the direction of the jejunum (Fig. 6A & B). However, the tube may be pulled through the pylorus and brought out of the anterior wall of the stomach, similar to a gastrostomy (Fig. 7A & B). Interrupted sutures of linen or silk then approximate the serosa of the duodenum to Glisson's capsule of the liver in the region of the intubation. Posterior and lateral sutures are tied before the anterior group is introduced. The area is then drained by rubber dams which emerge through a small right subcostal incision.

In the majority of our cases a complementary Kader Stamm jejunostomy for alimentation was performed, the enterostomy tube being drawn through a left lateral stab wound.

The immediate postoperative complications in cases of anastomosis of hepatic duct to the duodenum, or the suture of the liver to the intestine with hepatico-intestinal intubation, may be due to leakage at the site of the anastomosis which may result in a biliary or intestinal fistula, or a generalized peritonitis. Drainage has largely eliminated the latter as a complication. Occasionally there was a temporary seepage of bile which soon disappeared within a few days. In one of our cases, a debilitated female, 69 years of age, who had had three previous attempts at reconstructive procedures, the early and partial separation of the duodenum from the surface of the liver within 48 hours, resulted in a fatal peritonitis. In another case a dehiscence of the duodenal suture developed which terminated in a right subphrenic abscess and a massive empyema with multiple loculations. During the period in which the duodenal fistula was active, the intestinal secretions were aspirated by continuous suction and the chemical balances were regulated by the introduction of the aspirated contents, pabulum and electrolytes through the jejunostomy.

The use of the rubber tube in biliary duodenal intubation undoubtedly has some advantages and a few possible late disadvantages. The tube, because of its pliancy, is easy to handle and adapts itself to the mechanical conditions present. It relieves the obstructive jaundice. Its presence not only prevents an edema occluding the anastomotic site but in addition it acts as a supporting scaffold until the union between the duct and duodenum is firm. In the majority of reported cases, and in ours, the peristaltic activity of the intestine was sufficient ultimately to discharge the tube which was eventually passed by rectum in three to twelve weeks after operation. Some of the patients were unaware that the tube had been eliminated although x-ray examination failed to reveal its presence. On the other hand the tube may be retained indefinitely. It may be subsequently plugged with bile salts and then the resultant biliary stasis favors ascending infection. Judd[6] reported the retention of a tube for four years when a cholangitis developed which necessitated its removal two years later. However, innumerable occasions have been offered to examine tubes which have been retained for a year or more. Many of these are in a state of good preservation and

relatively free from encrustation and from the disintegrating effects of bile salts. Andrus[7] cited a case in which the tube had been in place for eight years and still seemed to be serving its initial purpose. It would seem desirable to be able to control the passage of the tube but older methods in which this was attempted were discarded because they were unsatisfactory. In one of our cases in which the distal end of the biliary duodenal tube was brought through the pylorus and then out of the stomach, so that theoretically it could have been withdrawn at will, the early development of a gastric fistula necessitated its removal on the eleventh day. The premature removal of the tube in this case at a time before a firm anastomosis had been established was probably the reason for an early recurrence of a secondary stricture and cholangitis.

Pearse,[8] in order to eliminate some of the objectionable features of rubber, used vitallium tubes of various sizes and shapes especially designed to meet the particular mechanical conditions encountered in strictures of the extra-hepatic ducts. He found that this metal did not corrode and bile salts did not precipitate on its walls. Experimentally he noticed that the mucous membrane lining the tube failed to show any reaction although the mucous membrane did not grow into the metal tube. But he added there was a general tendency for all tubes used in this work to eventually pass into the intestinal canal. Undoubtedly a metal tube, with a flange at its center and funnel shaped at one end, introduced into the hepatic duct, may remain in place and maintain its patency for a longer period of time than a rubber tube. However, recently Bettman and Tannenbaum[9] found it necessary to remove a 1 inch vitallium tube which they had implanted in a strictured common bile duct because the lumen was entirely plugged with a greenish deposit. Moreover, a rigid vitallium tube in certain locations may be more difficult to handle than rubber, and the use of vitallium per se will probably not reduce the incidence of ascending infection from regurgitation, even though it maintains an adequate lumen between the liver and the intestine.

In a group of seven patients in whom a hepatoduodenostomy with hepaticoduodenal intubation with a rubber tube was performed, there was one death from a generalized peritonitis due to a duodenal leak. Five of these patients have been previously reported in detail.[10] There were four patients who after an immediate postoperative period have remained well and have never experienced any clinical evidence of an

ascending infection. One patient has been followed for five years, one for three years, one for two years, and one for five months. In the remaining two patients, persistence of a mild icterus has been noted and attacks of Charcot fever have been frequent, in one for the past four years and in the other for about two and a half years. At the onset the attacks were partially ameliorated by stimulating the intestine and the flow of bile by the use of saline cathartics and the infection was partially controlled by the careful administration of chemotherapeutic and antibiotic agents. In both these patients a recurrent stricture with chronic cholangitis is probably present. One patient was re-operated without success and the other has refused further surgery.

This serious complication of ascending infection due either to a recurrent stricture with biliary stasis or to intestinal regurgitation into the biliary radicles of the liver is always a possibility in any reconstructive procedure of the hepatic or common bile ducts, especially in those instances in which the sphincter mechanism has either been side tracked or eliminated. Over twenty-five years ago Eliot[11] stated that "the dangers of ascending cholangitis varies directly with the distance from the site of the papilla through which a new opening in the intestine was made. The result of subsequent regurgitation of intestinal contents is small if the end of the divided duct or the rubber tube in cases of reconstruction is passed obliquely (Witzel) through the intestinal wall. The risk of postoperative leakage, the subsequent formation of a duodenal fistula is also diminished by this procedure. For the purpose of still further decreasing these postoperative complications, provisions may be made for the insertion of the end of the divided duct, or in cases of reconstruction, of the rubber tube into a portion of the small intestine which has been excluded from the path of the intestinal contents by a simple entero-anastomosis or by a more complicated procedure," i. e., the Roux principle of intestinal anastomosis. At that time this procedure was rarely performed because the general condition of the patient did not permit a prolonged operation in view of the longstanding pre-existing jaundice. Today, however, the preoperative use of vitamin K, transfusions of blood and plasma, and the high protein and carbohydrate diet have practically eliminated the dangers of cholemia and have made these prolonged operations feasible.

In intractable cases of ascending infection following previous reconstructive procedures, it may become imperative to divert the flow

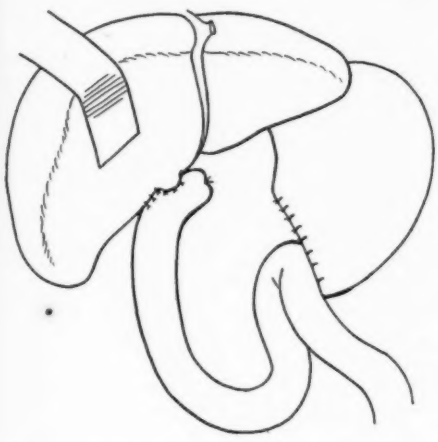

Fig. 8.—Subtotal gastrectomy of Billroth II type following hepaticoduodenostomy.

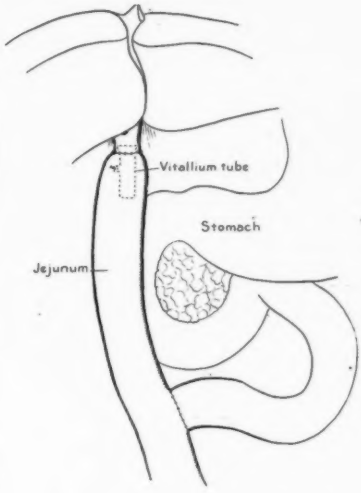

Fig. 9.—Hepaticojejunostomy over a vitallium tube with Roux Y type of intestinal anastomosis.

of the intestinal contents and eliminate the factor of regurgitation. In cases in which a hepaticoduodenostomy has been done, Finsterer suggested that the gastric contents should be side tracked by a subtotal gastrectomy of the Billroth II type (Fig. 8). This was done in one of our cases without any relief, but it is likely that this procedure was ineffectual because the infection had already become too firmly entrenched in the finer biliary ducts of the liver. The seriousness of ascending infection has been vividly re-emphasized in the past few years in those cases in which the enlarged gallbladder was anastomosed to the stomach following radical resections of the duodenum and the pancreatic head. In an effort to diminish the incidence of cholangitis and multiple liver abscesses which often terminated fatally, the severed dilated common duct was implanted into a loop of jejunum in which the food current was diverted either by an entero-enterostomy or preferably by a Roux Y type of intestinal anastomosis performed at some distance from the point of implantation. This latter procedure, advocated by Whipple,[12] Child,[13] and others, seems to have materially reduced the incidence of the Charcot syndrome. Recently, Cole, Ireneus, and Reynolds[14] have reported several cases in which the choledochus was almost

completely destroyed and in which a vitallium tube inserted in the hilar stump was anastomosed to the single arm of the jejunum utilizing the Roux principle. Then to further reduce the amount of intestinal regurgitation a series of intraluminal jejunal valves was constructed. This procedure has apparently eliminated attacks of cholangitis. The operation described by Coe was recently used in a case of biliary bronchial fistula secondary to a stricture of the hepatic duct. Unfortunately this patient developed a secondary hemorrhage on the second day from an arterial vessel injured at the time of operation, and she succumbed nine days after operation. There was no post mortem. The second patient, aged 22, was operated upon recently by P. Klingenstein.[15] She presented a stricture at the porta hepatis and following the implantation of a vitallium tube into the blind jejunal loop she made a good recovery and at present is convalescent. No further x-ray studies with barium have been made.

Comment

As the literature of reconstructive procedures for strictures of the common and hepatic bile ducts is reviewed, and one's personal experiences are studied, certain depressing facts become apparent. It is evident that the operation of cholecystectomy is not a simple innocuous procedure because the most frequent cause of benign stricture is the accidental injury of the ducts during the removal of the gallbladder. Stricture of the extra-hepatic ducts resulting in biliary obstruction and infection is an exceedingly serious condition. Various plastic procedures designed to restore biliary intestinal continuity are extremely difficult and are attended by an appreciable operative mortality. Furthermore, the follow-up studies of these patients reveal that many suffer from the effects of the local reformation of scar tissue and from ascending infection. Therefore, any reconstructive procedure which will maintain the calibre of the duct and the sphincter mechanism is greatly to be desired. Unfortunately the pathology in the majority of cases makes this impractical. In many cases it becomes necessary to anastomose the extrahepatic duct or its hilar stump preferably to the duodenum or the jejunum over a tube. For intubation, rubber, vitallium, or tantalum may be used. Biliary intestinal intubation provides the immediate relief of the obstructive jaundice and should act as an intraluminal support until the anastomosis is firmly healed. The vitallium tube is favored at present

because it is retained longer, and is less apt to be clogged by the precipitation of bile salts but its presence per se does not diminish the incidence of either duodenal or jejunal regurgitation, a factor in the production of the Charcot syndrome. The reason why certain patients will develop attacks of ascending cholangitis in the presence of an adequate biliary intestinal fistula is not clear. The fact that some of these patients may be subsequently relieved of cholangitic episodes by secondary operative procedures in which the intestinal current is diverted and the degree of regurgitation reduced raises an important question. Should the operation of hepaticoduodenostomy or hepatoduodenostomy with hepaticoduodenal intubation be continued as a primary procedure, performing at a later date if necessary a subtotal gastrectomy of the Billroth II type to divert the gastric contents in cases of ascending infection, or should these cases be treated initially by hepaticojejunostomy or hepatojejunostomy with intubation, utilizing the Roux principle of intestinal anastomosis with the hope that the primary diversion of the intestinal content will lessen the incidence of cholangitis? This is a fundamental problem which only the following results in these respective groups of surgical procedures will decide.

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THE TREATMENT OF SEASONAL AND NON-SEASONAL HYPERESTHETIC RHINITIS WITH ANTHALLAN*

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IN THE practice of rhinology, one of the most distressing symptom complexes, both to the patient and his physician, is the chronic hypersensitive nose. The characteristic symptoms of this condition are sneezing, watery nasal discharge, itching of the nose or eyes, and intermittent nasal obstruction. The physical signs are a change in the color of the mucous membrane, increased nasal secretion, and increased thickness of the mucosal lining. Microscopic examination of the secretion shows the absence of bacteria and the presence of excess numbers of eosinophiles, and roentgenograms and lavage of the sinuses show absence of infection. Infection of the nasal mucosa and the paranasal sinus mucosa can produce a similar symptom complex to that found in the hypersensitive nose, and it may exist concurrently in patients with a hypersensitive nose. However, all cases in which infection of the upper respiratory tract could be demonstrated were excluded from this study.

Williams[1] describes "chronic hypersensitive nose," named by him "intrinsic allergy," as "a fundamental, inherited, localized, cellular abnormality, resulting in some change in the cellular permeability and concomitant release of histamine when the deficient cell is affected by stimuli which obtain little or no response from the normal cell." Best and McHenry[2] state that the release of histamine into the tissue of animals produces arteriole constriction, capillary dilation, and subsequently, edema in the area as the permeability of the capillary walls increases. Many factors which elicit or influence this response have been studied clinically and experimentally, and evidence exists to show that one or more of the following influences also plays a part in cases of

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chronic hypersensitive nose: specific allergens demonstrated by skin testing, endocrine dysfunction, psychopathic personality, physical agents such as heat, cold, and humidity, and local and systemic infection.

The complicated nature of the problem presented by each individual having this symptom complex makes an accurate diagnosis difficult. Many physicians have no access to adequate laboratory facilities and x-ray apparatus. Moreover the average patient cannot afford the expense of adequate skin testing, a psychiatric study, or a series of special laboratory examinations. The unsatisfactory diagnostic aspect is paralleled by an unsatisfactory status of treatment. Many patients undergo a period of extensive testing in the search for specific allergens, followed by another period during which desensitization by means of specific allergic substances or nonspecific agents is used in an attempt to relieve the symptoms. This procedure is time consuming, and not always successful. Rhinologists of the conservative school have relied upon the local application of vasoconstrictors, the administration of sedatives, and the application of caustics to the nasal mucosa. The members of a more radical group cauterize the turbinate bodies, trim them surgically, and straighten the septum in the attempt to create more air space in the nose. The most radical approach to the problem is to remove the turbinate bodies, exentrate the ethmoid sinuses, and remove the lining of the maxillary and sphenoid sinuses. In general, only temporary, partial relief is obtained by topical application or by surgical treatment.

Anthallan, 3'di(n-butyl)amino-methyl-1,4,5,6-trihydroxy-benzo(1,2,-c)furan-1'(3')-one, which is administered by mouth, makes possible an entirely different management of this type of case. Not only can hyperesthetic rhinitis be treated simply and effectively with this drug, but the diagnostic problem can be ignored. This report was prompted by the impressive results obtained in the treatment of 108 cases of seasonal and non-seasonal hyperesthetic rhinitis in private practice, and also by the success reported in the treatment of neurodermatitis disseminata and urticaria[3] with Anthallan.

According to one of the investigators, this drug showed its capacity to decrease the threshold sensitivity to histamine. However, this property alone does not explain sufficiently its action in the treatment of hyperesthetic rhinitis.

The toxicologic data submitted with this drug indicate that the drug has a low toxicity, e.g., the median lethal dose for the enterally

administered drug is over 3.0 gm. per kilogram in the mouse, over 2.0 gm. per kilogram in the dog, and over 1.0 gm. per kilogram in cats, guinea pigs and rabbits. A high multiple of the therapeutic dose, given daily over periods of 1 to 2 years, was tolerated by rats, guinea pigs and mice with no changes demonstrable in microscopic pathology. In studies of blood and urine performed during and at the termination of these long-term feeding experiments with Anthallan at dosage levels up to 200 mg. per kilogram daily, no significant differences in body-weight were found between controls and Anthallan-fed animals, with respect to blood cell count, blood formation, blood cell picture, blood sugar level, or kidney function.

It is well known that the severity of the symptoms of hyperesthetic rhinitis in a given individual varies from season to season, from day to day, and often from hour to hour, so that the cyclic fluctuation is often unpredictable. For this reason a careful selection of cases was believed to be of utmost importance in order to obtain conclusive information about the effectiveness of this drug. The patients studied were selected from those attending the Outpatient Department of the Otolaryngological Service of the Columbia University Presbyterian Hospital Medical Center. All patients so selected to whom a course of Anthallan treatment was given are included in this study. Criteria for selection follows:

1. Patients were selected who gave a history of persistent nasal obstruction and who showed the physical signs of increased nasal secretion, decreased breathing space, and a change in the color and appearance of the nasal mucosa. Patients in whom infection or mechanical obstruction of the nose could be found were eliminated after the first examination.

2. Patients who showed no gross evidence of upper respiratory infection, but whose nasal secretion contained an excessive number of bacteria or inflammatory cells were not accepted.

3. Patients in whom roentgen examination showed the presence of normal sinuses or sinuses with minimal thickening of the lining membrane were accepted, while those with a diagnosis of clinical sinusitis were not accepted.

4. Patients with an active systemic disease such as syphilis, nephritis, diabetes or infectious bronchitis were not considered acceptable.

Patients were selected whose symptoms had existed for a long period of time, the average being 506 days, prior to this study. No patient was

selected for study at a time of year during which he was usually free from symptoms or at a time when his condition in former years had had a tendency to improve. Although the cases selected satisfied the diagnostic criteria for hyperesthetic rhinitis, some individual differences were apparent. The following table shows that some patients were sensitive to specific allergens. It also shows the number of patients whose hyperesthetic rhinitis was seasonal, non-seasonal, and both.

It was difficult to select a name for the condition these patients had in common. The following names under which these cases have been listed in general usage were discarded: "Nonseasonal hayfever," "physical allergy," "allergic rhinitis," "nasal allergy," "intrinsic allergy;" all imply the presence of an allergen, yet in many cases no allergen can be demonstrated. "Chronic Rhinitis" implies the presence of an inflammatory process, yet in many cases no infection can be shown. "Vasomotor Rhinitis" places the emphasis on the instability of the blood flow, but disregards the lymphstasis. A name was desired which would permit the inclusion in this study of cases in which a specific allergen had been found. Seasonal and non-seasonal "*Hyperesthetic Rhinitis*," has been chosen as the most descriptive name because, first, it suggests the element of hypersensitivity of the nasal mucosa; secondly, perennial and seasonal cases may be included; and third, it implies the symptoms of excessive nasal discharge, excess sneezing, and nasal obstruction of which these patients complain.

Conditions were controlled as much as possible during the experiment. No patient was allowed to change any factors such as his surroundings, diet, or activities which might conceivably affect the severity of the nasal symptoms. Therefore, any remission of these symptoms during Anthallan therapy can be attributed only to the influence of this drug.

In order to make the evaluation of the subjective symptoms and the clinical findings as unbiased as possible, several observers examined each patient each week. They took into consideration only those phenomena which can be expected to respond to a drug; these "responsive features" are the patient's statement about his symptoms, the color of the mucous membrane, the amount of breathing space, and the amount of visible secretion in the nose. The observer gave each of these essential symptoms a numerical value, using a scale of 5 grades, 0 to 4, which was entered in a rating chart. In order to determine the percentage of

Table I

ALLERGEN SENSITIVITY IN 42 PATIENTS WITH HYPERESTHETIC RHINITIS

	Cases	*Percentage*
Specific allergens found by skin testing	16	38%
No allergens found by skin testing	3	7%
Not tested	23	55%
Total	42	100%
Seasonal Hyperesthetic Rhinitis	4	9.3%
Nonseasonal Hyperesthetic Rhinitis*	31	76.2%
Seasonal and Nonseasonal Hyperesthetic Rhinitis	7	14.5%
Total	42	100%

* One case of nonseasonal hyperesthetic rhinitis was limited to a portion of the menstrual cycle.

Table II—SUMMARY OF SIX PATIENTS WHO DID NOT COMPLETE THE COURSE OF ANTHALLAN THERAPY

Case No.	*Cause for Stopping Treatment*	*Duration of Disease*	*Treatment Days*	*Improvement on Last Examination*
1	Acute bronchopneumonia	47 days	7	Exam. 2 mo. later 100% relief
2	Skipped one week	96 days	14	90% relief
3	Contradictory statements	"years"	21	75% relief
4	Refused to return to clinic	10 years		
5	Contradictory statements	240 days	7	50% relief
6	Bilateral purulent antral sinusitis	10 years		0

improvement after Anthallan treatment, a patient's average rating for a single day's examination was compared with his average rating before treatment. Since the numerical evaluation does not always express the whole clinical impression of the patient's condition, a short statement, called "medical estimate," was also made at the time of each examination.

Forty-eight patients were selected according to the diagnostic criteria, from a great number submitted by the resident staff, attending staff, and by personal application. Six of the patients who failed to complete the course of treatment in the manner prescribed had to be eliminated from the series as inconclusive. However, Table II shows that the response of these six patients who did not complete the course of Anthallan was comparable to the response of the conclusive cases.

Table IIA—INFLUENCE OF ANTHALLAN UPON SEASONAL AND NONSEASONAL HYPERESTHETIC RHINITIS

Improvement During Anthallan Treatment Recorded on Numerical Rating Chart

Case	*Duration of disease y-years m-months*	*Age (years)*	*Duration of present attack (days)*	*Treatment (days)*	*Dosage (capsules)*
1	12 y	16	30	21	153
2	3 y	21	130	35	225
3	16½ m	13	496	13	60
4	6 y	31	60	21	126
5	4 y	18	1.200	28	154
6	1 y	12	360	21	149
7	2 y	42	720*)	21	98
7a**)	—	—	—	14	112
8	6 y	13	1.080	21	119
9	3 y	17	1.080	21	133
10	3 y	34	1.080	21	133
11	2 y	21	720	28	154
12	4 y	30	1.440	7	35
13	4 m	28	120	14	77
14	6 m	42	180	21	175
15	5 m	37	150	21	92
16	5 y	27	1.800	21	170
17	8 y	45	360	26	166
18	2 m	44	70	21	133
19	9 m	27	270	35	220
20	8 m	12	240	7	35
21	5 y	13	720	28	231
22	4½m	40	135	21	151
23	8 y	10	210	21	133
24	3 y	37	1.080	21	161
24a**)	—	—	—	21	154
25	20 y	39	390	21	168
26	4½ y	40	77	21	147
27	4 m	58	120	21	166
28	2½ y	39	540	21	88
29	20 y	42	360	14	77
30	1 y	39	11	21	136
31	2½ y	20	900	28	161
32	3 y	26	1.080	21	133
33	6 y	40	R***)	21	133
34	3 m	30	90	21	133
35	25 y	40	R	21	133
36	8 m	28	240	28	203
37	18 m	25	540	14	84
38	5 m	37	150	21	133
39	26 y	57	R	21	146
40	5 y	35	R	28	190
41	2 y (42)	27 (42)	R (36)	16 (44)	108 (44)
42	R	44	R	16	130
Total	200.2	1,296	18,229	925	6,048
Average	4¾ y	31	506	21	137

*) This case had symptoms for two years regularly at every menstrual period for 6 days; 3 days before and after the onset of menstruation (see individual case report).

**) Repeat course of Anthallan.

***) R: Ragweed Hayfever.

Table IIB—INFLUENCE OF ANTHALLAN UPON SEASONAL AND NONSEASONAL HYPERESTHETIC RHINITIS

Improvement During Anthallan Treatment Recorded on Numerical Rating Chart

Case	End of Anthallan Treatment		
	Complaints	*Physical Examination*	*Medical Estimate*
1	86	100	85
2	100	86	75
3	100	100	100
4	100	100	100
5	83	66	80
6	75	75	50
7	76	75	75
7a**)	90	77	100
8	100	100	100
9	78	100	100
10	78	90	90
11	83	82	80
12	100	100	100
13	100	100	100
14	0	0	0
15	83	100	100
16	71	67	75
17	69	50	50
18	38	83	75
19	86	75	75
20	96	100	100
21	75	75	75
22	28	30	40
23	86	100	100
24	89	88	90
24a**)	—	—	100
25	87	70	75
26	66	63	60
27	25	83	75
28	12	17	0
29	70	100	100
30	0	0	0
31	50	47	80
32	96	80	90
33	100	100	100
34	70	67	75
35	95	75	75
36	95	100	100
37	75	100	75
38	0	0	0
39	54	37	30
40	87	64	50
41	100 (43)	100 (43)	100 (44)
42	95	100	100
	3,149	3,022	3,310
	73	70	75

**) Repeat course of Anthallan.

Table IIC—INFLUENCE OF ANTHALLAN UPON SEASONAL AND NONSEASONAL HYPERESTHETIC RHINITIS

Improvement During Anthallan Treatment Recorded on Numerical Rating Chart

Persistence of Therapeutic Result in Post-Treatment Period			
	First Observation		
Case	*Complaints*	*Physical Examination*	*Medical Estimate*
1	100	100	100
2	100	71	75
3	100	100	100
4	78	75	50
5	72	100	90
6	50	50	50
7	50	50	50
7a**)	100	100	100
8	90	94	75
9	67	83	40
10	—	—	—
11	83	82	80
12	100	100	100
13	—	—	—
14	0	0	0
15	83	83	75
16	71	—	75
17	33	25	25
18	87	100	75
19	86	75	90
20	96	100	100
21	58	69	75
22	40	40	40
23	100	100	100
24	89	88	85
24a**)	—	—	—
25	—	—	—
26	66	75	60
27	92	100	100
28	—	—	—
29	—	—	—
30	—	—	—
31	15	47	20
32	96	80	100
33	100	100	100
34	70	67	75
35	95	88	95
36	55	50	50
37	100	100	100
38	0	0	0
39	87	73	75
40	—	—	—
41	— (34)	—	— (34)
42	— [33]	— [33]	— [33]
	2,509		2,425
	[2,438]	[2,335]	[2,350]
	74		71
	[74]	[71]	[71]

**) Repeat course of Anthallan.

xxxx) In [ ] parenthesis: re-examined cases only.
In ( ) parenthesis: number of cases in individual column.

Table IID—INFLUENCE OF ANTHALLAN UPON SEASONAL AND NONSEASONAL HYPERESTHETIC RHINITIS

Improvement During Anthallan Treatment Recorded on Numerical Rating Chart

Case	Persistence of Therapeutic Result in Post-Treatment Period: *Second Observation* — *Complaints*	*Second Observation* — *Physical Examination*	*Second Observation* — *Medical Estimate*	*Interval from End of Anthallan Treatment to Last Post-Observation Entry (days)*
1	86	100	100	54
2	61	71	75	40
3	100	100	100	248
4	—	—	—	27
5	—	—	—	7
6	43	50	50	34
7	—	—	—	14
7a**)	70	77	75	89
8	90	94	75	118
9	—	—	—	34
10	—	—	—	—
11	100	100	100	78
12	—	—	—	14
13	—	—	—	7
14	0	0	0	—
15	83	92	90	141
16	—	—	—	20
17	—	—	—	14
18	100	100	95	86
19	86	75	75	56
20	100	100	100	55
21	96	100	90	34
22	40	40	40	35
23	100	100	100	105
24	84	76	75	103
24a**)	—	—	—	—
25	—	—	—	—****)
26	97	100	76	30
27	92	83	75	74
28	—	—	—	—
29	—	—	—	—
30	—	—	—	—
31	—	—	—	7
32	79	70	75	48
33	—	—	—	21
34	85	50	75	21
35	—	—	75	34
36	50	63	75	21
37	—	—	—	21
38	—	—	—	14
39	—	—	—	7
40	—	—	—	—
41	—	—	—	—
42	— [21]	— [21]	— [21]	— [35]
	1,640	1,641	1,616	1,711
	[78]	[78]	[77]	50

**) Repeat course of Anthallan.
xxxx) In [ ] parenthesis: re-examined cases only.
****) (patient went abroad at end of Anthallan treatment.)

Table III—SURVEY OF INFLUENCE OF ANTHALLAN UPON 42 CASES (44 COURSES) OF SEASONAL AND NON-SEASONAL HYPERESTHETIC RHINITIS

	Total	*minimum*	*maximum*	*average*
number of Cases	42	—	—	—
number of Anthallan Courses	44	—	—	—
age (Years)	—	10	58	31
duration of Disease (years)	—	1/6	26	4¾
duration of present Attack (days)	—	11	1800	506
duration of Anthallan treatment (days)	—	7	35	21
dosage (capsules .085 Gm. Anthallan)	—	35	231	137

	number of courses	*percentage of all courses, showing* complete disappearance of symptoms*)	very satisfactory improvement**)	fair improvement***)	failure****)	*number of cases in which improvement* increased	decreased	stayed same	*Average per cent improvement cases in all*
		(In parenthesis: number of cases)				*compared with status at end of anthallan period*			
A. result at end of anthallan treatment, as rated from:									
a. "Complaints"	43	19(8)	56(24)	16(7)	10(4)	—	—	—	73
b. "Physical Examination"	43	38(16)	33(14)	19(8)	10(4)	—	—	—	70
c. "Medical Estimate"	44	37(16)	41(18)	11(5)	9(4)	—	—	—	75
B. result at first re-examination in post-treatment period, as rated from:									
a. "Complaints"	34	23(8)	44(15)	23(8)	9(3)	8	9	16	74
b. "Physical Examination"	33	33(11)	36(12)	23(8)	6(2)	8	11	14	71
c. "Medical Estimate"	34	30(10)	39(13)	21(7)	9(3)	8	9	17	71
C. result at second re-examination in post-treatment period, as rated from:									
a. "Complaints"	21	24(5)	52(11)	19(4)	5(1)	8	7	6	76
b. "Physical Examination"	21	38(8)	38(8)	19(4)	5(1)	4	5	12	78
c. "Medical Estimate"	21	24(5)	62(13)	9(2)	5(1)	5	6	10	76

*) — 100% improvement
**) — 70 to 99% improvement
***) — 25 to 69% improvement
****) — less than 25% improvement

Table IVA—LABORATORY STUDIES

Case	Sex	Hb %		Blood Cell Count RBC		WBC	
		a	*b*	*a*	*b*	*a*	*b*
1	F	96	90	4,590,000	4,370,000	6,000	5,600
2	F	90	89	4,540,000	4,450,000	5,250	4,050
3	F	100	108	4,610,000	4,900,000	7,200	7,000
4	F	104	90	5,120,000	4,490,000	9,000	9,400
5	F	92	92	4,180,000	4,510,000	6,800	5,900
6	F	88	84	4,030,000	4,210,000	5,800	7,000
7	F	90	82	4,380,000	4,460,000	8,650	7,950
8	M	90	88	4,510,000	4,620,000	6,750	5,500
9	F	100	—	4,650,000	—	6,800	—
10	M	84	—	3,710,000	—	5,900	—
11	F	84	—	4,420,000	—	10,150	—
12	F	102	—	4,910,000	—	5,950	—
13	F	100	91	4,860,000	4,300,000	7,400	9,280
14	F	80	79	4,630,000	4,490,000	5,300	5,400
15	F	88	101	4,450,000	4,820,000	5,800	6,400
16	F	100	—	5,950,000	—	7,450	—
17	F						
18	M	96	87	4,720,000	4,520,000	6,100	7,310
19	F						
20	F	81	82	4,350,000	4,080,000	6,700	6,650
21	F	87	87	4,510,000	4,400,000	4,150	6,150
22	F						
23	M	101	80	4,890,000	3,940,000	9,900	6,450
24	M	96(22)	93	4,280,000(22)	4,800,000	5,750(22)	4,650
25	M	88[17]	86[17]	4,000,000[17]	4,000,000[17]	5,100[17]	4,600[17]
Total**)		2137		100,290,000		147,900	
		[1567]	1509	[76,650,000]	75,360,000	[111,650]	109,090
Average:		97		4,559,000		6,720	
		[92]	[89]	[4,509,000]	[4,433,000]	[6,568]	[6,417]

a: Test before Anthallan treatment.
b: Test near end of Anthallan treatment.
**) In [ ] parenthesis: re-examined cases only.

The remaining forty-two patients each received a course of Anthallan. Two patients had a recurrence of symptoms, and received a second course of the drug, and all cases satisfy the diagnostic criteria of hyperesthetic rhinitis. Many of the cases were patients at the Vanderbilt Clinic for a number of years and repeated studies by the staff, or by personal physicians, had established the presence of specific sensitivities in some of these cases.

The individual therapeutic results are surveyed in Table II A-C. Every change in the nasal manifestations observed during the period of treatment with Anthallan can be attributed to the influence of the drug. In all cases the Anthallan treatment period was considerably shorter than the period during which the manifestations had existed.

The percentage distribution of improvement obtained during Anthallan treatment is surveyed in Table III, upper part. In addition, the results observed during Anthallan administration are compared in Table III, lower part, with those recorded after termination of the treatment. Only four cases were failures, including all degrees of improvement up to 24 per cent, a very low number, being less than 10 per cent of all the cases. The percentage of patients experiencing complete or practically complete relief from symptoms amounted to about 36 per cent* during the course of therapy. An improvement of 70 per cent or more occurred in 56 per cent of the cases at the end of Anthallan treatment. This result persisted as far as could be judged from most of the patients who were available for reëxamination at various post-treatment periods. The persistency of the result obtained during Anthallan treatment is shown in the lower part of Table III. Only about 30 per cent* of all cases showed any tendency to relapse after two post-treatment examination periods, of one month or more, and even in these cases a considerable degree of improvement was still retained. In other words, there was never a case showing a complete relapse (except Case No. 24 which is reported in detail later.) On the average, the improvement observed about 7 weeks after discontinuation of the drug compares favorably with the improvement shown at the end of the Anthallan period. The fact that there is an undeniable degree of persistence of the beneficial effect of Anthallan for a period after the administration is discontinued adds to the value of this drug.

The results were obtained within periods of treatment of an average length of 21 days. In 7 cases the treatment periods were considerably shorter, 7 to 14 days. Frequently, the degree of improvement recorded at the end of the Anthallan treatment period could be observed within the first 4 or 5 days of therapy.

The usual dose required to obtain these improvements was 6 capsules (each capsule 0.085 gm.) daily during the first week of treatment;

* Varying according to whether the estimate is based upon "Complaints," "Physical Examination" or the comprehensive "Medical Estimate."

Table IVB—LABORATORY STUDIES

Blood Cell Count

Case	*Polym.* %		*Lymph.* %		*Baso.* %		*Monoc.* %		*Eos.* %	
	a	*b*	*a*	*b*	*a*	*b*	*a*	*b*	*a*	*b*
1	59	50	36	41	0	1	4	7	1	1
2	56	51	33	33	0	1	7	8	7	7
3	61	61	25	26	1	0	5	6	8	7
4	74	72	0	25	0	0	9	3	17	0
5	52	64	33	28	0	0	9	5	6	3
6	49	59	40	29	1	1	5	5	5	6
7	78	71	16	25	1	2	5	2	0	0
8	53	54	23	30	1	0	8	3	15	13
9	65	—	27	—	0	—	7	—	1	—
10	48	—	38	—	1	—	7	—	6	—
11	57	—	26	—	1	—	7	—	9	—
12	55	—	36	—	0	—	6	—	3	—
13	66	59	24	29	0	1	4	6	6	5
14	45	61	35	29	2	0	7	3	9	7
15	60	65	28	22	0	1	11	9	1	3
16	83	—	12	—	0	—	5	—	0	—
17	—	—	—	—	—	—	—	—	—	—
18	58	59	32	26	0	0	6	2	4	13
19	—	—	—	—	—	—	—	—	—	—
20	44	71	37	24	0	0	9	1	10	4
21	41	54	45	35	1	0	2	6	11	5
22	—	—	—	—	—	—	—	—	—	—
23	66	57	24	36	1	1	5	5	4	1
24	60(22)	55	28(22)	35	1(22)	1	4(22)	5	7(22)	4
25	44[17]	51[17]	44[17]	46[17]	0[17]	0[17]	7[17]	1[17]	5[17]	2[17]
Total	1274	—	642	—	11	—	139	—	135	—
	[966]	1014	[503]	519	[9]	[9]	[107]	[77]	[116]	[79]
Average:	58	—	29	—	0.5	—	6	—	6	—
	[57]	[60]	[30]	[30]	[0.5]	[0.5]	[6]	[4.5]	[7]	[5]

a: Test before Anthallan treatment.
b: Test near end of Anthallan treatment.
**) In [ ] parenthesis: re-examined cases only.

Table IVC—LABORATORY STUDIES

Case	Blood Chemistry: Glucose mg%		Blood Chemistry: NPN mg%		EKG	
	a	*b*	*a*	*b*	*a*	*b*
1	91	90	20	37	—	—
2	99	83	20	15	normal	normal
3	93	—	20	—	LD*)	no change
4	87	—	22	—	normal	normal
5	86	90	21	21	normal	normal
6	90	92	19	18	—	—
7	85	86	22	25	normal	normal
8	92	88	23	24	normal	normal
9	86	—	25	—	—	—
10	96	—	23	—	—	—
11	86	—	21	—	normal	normal
12	96	—	28	—	—	—
13	95	103	20	23	—	—
14	—	81	—	22	—	—
15	92	78	19	21	normal	normal
16	89	89	29	20	normal	normal
17						
18	93	114	29	26	normal	normal
19						
20	71	98	18	23	SA*)	no change
21	85	83	21	24	normal	normal
22	95	96	22	21		—
23	94	87	20	25	RD*)	no change
24	97(22)	91	34(22)	34	normal	normal
25	99[17]	91[17]	25[17]	23[17]	normal	normal(15)
Total**)	1997 [1453]	[1540]	501 [362]	[402]		
Average	90 [90]	[90]	23 [23]	[24]		

a: Test before Anthallan treatment.
b: Test near end of Anthallan treatment.
*) LD—Left Axis Deviation.
RD—Right Axis Deviation.
S.A.—Sinus Arrythmia.
**) In [ ] parenthesis: re-examined cases only.

Table V—INFLUENCE OF ANTHALLAN UPON NASAL SMEAR EOSINOPHILES AS COMPARED WITH BLOOD EOSINOPHILES

No. of Case	*Eosinophiles Nasal Smear*)*		*Eosinophiles Blood Count*	
	a	*b*	*a*	*b*
1	2	2	1	1
2	7	7	7	7
3	0	0	8	7
4	2	2	17	0
5	2	0	6	3
6	0	0	5	6
7	0	0	0	0
8	2	0	15	13
9	2	2	1	—
10	2	2	6	—
11	0	1	9	—
12	0	0	3	—
13	7	7	6	5
14	7	10	9	7
15	10	0	1	3
16	0	10	0	—
17	7	7	—	—
18	10	2	4	13
19	10	10	—	—
20	7	7	10	4
21	10	2	11	5
22	10	2	—	—
23	10	10	4	1
24	10	10	7(23)	4
25	10(25)	7(25)	5[16]	2[16]
Total**)	127	100	135	—
	—	—	[109]	[81]
Average	5	4	6	—
	—	—	[7]	[5]

a: Test before Anthallan treatment. b: Test near end of Anthallan treatment.

*) Explanation of Rating of Nasal Smear: Rated as:

None seen:	0
Between one and four, per field from at least six oil immersion fields in separate areas of the slide:	2
Between five and nine, as above:	7
Ten or more, as above:	10

**) In [ ] parenthesis: re-examined cases only.

this dose varied during the subsequent weeks between 3 capsules and 12 capsules daily according to clinical response. The dose did not have to be varied to any degree according to the age or sex of the patient. Altogether the average dose was about 7 capsules daily.

A collateral study of the clinical toxicity of the drug was carried on in the first twenty-five cases by laboratory studies of the blood count, urinalysis, blood chemistry, and nasal smear both before and after treatment. Electrocardiograms were taken before and at the end of Anthallan treatment in representative cases. During the weekly clinical examinations special attention was devoted to any symptoms or signs of side-effects of the drug, such as headache, vertigo, nausea, vomiting, diarrhea and skin rashes.

These laboratory tests and clinical observations were made during the course of Anthallan treatment to determine whether the drug in any way influenced the patient's normal picture. The results of these tests are shown in Table IV and Table V. Table IV indicates that glucose and N.P.N. determinations, as well as hemoglobin, blood counts, urinalysis and electrocardiograms all remain essentially unchanged during and following treatment with Anthallan. Kline tests were also carried out routinely.

A comparison between nasal smear eosinophiles and blood eosinophiles, as recorded in Table V, showed no consistently parallel influence of Anthallan.

Clinical observations of possible toxic symptoms were essentially negative. Only 2 patients reported some side-effects during the period of treatment with Anthallan. One patient developed, at the end of the second week, a transitory fine macular rash which disappeared in 24 hours. One other patient developed diarrhea when taking 6 capsules daily, but was relieved by decreasing the dose to 4 capsules daily.

Case Reports: The following three cases are typical of those treated during this study:

Case No. 3: C.C., a 13 year old white schoolgirl of Spanish extraction complained of daily attacks of sneezing, watery nasal discharge, and intermittent nasal obstruction during the past 17 months. All tests of foods and inhalants made in the allergy clinic were reported negative. The symptoms were aggravated in the morning, by changes in temperature, and during the winter months.

Physical examination of the nose and throat showed that there was

no mechanical obstruction to breathing, but that the nasal mucosa was paler than normal, was bathed in clear watery nasal discharge, and was thickened. Roentgenogram and clinical study of the nasal sinuses failed to show any evidence of infection. Blood count, blood chemistry, blood serology, urinalysis, and electrocardiograms were normal.

Sixty capsules (5 grams) of Anthallan were administered for 13 days. At the end of the treatment period the patient reported complete relief of symptoms. Physical examination of the nose showed that the mucosa appeared normal. All laboratory examinations were repeated, and no significant change was found (see tables). The patient experienced no objectionable signs or symptoms during the treatment period. Four reëxaminations made during the first 9 months of the post-treatment period showed that the patient remained symptom free.

Case No. 20: G.L., a 12 year old Negro schoolgirl, complained of daily attacks of itching of the nose and throat, associated with sneezing, watery nasal discharge and almost continuous nasal obstruction. All symptoms were aggravated by damp weather. The patient did not associate her symptoms with any infection, activity, food, wearing apparel, or inhalants. Nose drops gave temporary relief. No skin testing for allergens had been performed.

Physical examination shows the nasal cavity to be filled with watery secretion, and the mucosa to be pale and boggy. The septum was deflected, with a spur in the right inferior meatus. There was no other mechanical obstruction. Laboratory studies, and roentgenograms failed to show any evidence of infection.

After 35 capsules (4 gm.) of Anthallan were administered during 7 days, the patient stated that she was completely relieved of all symptoms, and physical examination confirmed this statement. The routine laboratory examinations made before and after the treatment showed no variation from normal (see tables). Five reëxaminations were made in the first 10 weeks of the post-treatment period, and the complete relief from symptoms continued.

Case No. 24: F.H., a 37 year old baker of German extraction, complained of very severe attacks of sneezing, watery nasal discharge, and almost total nasal obstruction. He had been tested and was found sensitive to wheat and rye flour, and during the eight-hour work day in the bakery the symptoms were aggravated, but he was never completely relieved of symptoms during the 16 hours of the day that he was not

in contact with the flour. Desensitization gave no relief, but nose drops gave temporary relief. The severity of the symptoms increased during the humid weather.

Physical examination showed the presence of a slight conjunctivitis. Clinical study and roentgenogram of the sinuses failed to demonstrate any infection. There was extreme pallor of the nasal mucosa which was bathed in a tenacious clear secretion. There was also marked swelling of the mucosa but no polypoid change was seen. There was some deflection of the nasal septum without mechanical obstruction of the breathing space. A routine laboratory study showed normal values for blood count, blood chemistry, serology, urinalysis, and normal electrocardiograms.

Anthallan was given at the rate of 35 capsules the first week, 56 the second week and 70 the third week. During this period the patient continued to work in the bakery at his usual job. There was a steady improvement in the physical signs and symptoms during the 21 day period during which he took a total of 161 capsules (13.7 gm.). No objectionable symptoms or side-effects were experienced, and laboratory studies repeated at the close of the treatment showed no significant change (see tables).

The patient and the observers agreed on the estimate that about 90 per cent relief of symptoms occurred during the administration of the Anthallan. During the first 6 weeks of post-treatment observation the patient continued his work as a baker with a gradual return of symptoms about 5 weeks after completion of Anthallan course. However, he estimated that 75 per cent of the improvement originally gained was maintained. During the seventh week all of his symptoms returned to their full intensity, and he returned for a second course of treatment. All of the physical findings were present on the second as on the first examination.

Anthallan was again administered, and after 18 capsules taken during 3 days the symptoms were again relieved, to the extent of about 90 per cent. During a period of 28 days he took 158 capsules (12.9 gm.) and has experienced about 100 per cent relief.

Three other cases* are mentioned briefly because they illustrate the necessity of accurate diagnosis of associated conditions. One patient was a woman fifty-six years old who complained of the symptoms and

* Not treated in the Vanderbilt Clinic Series.

had the signs of a non-seasonal hyperesthetic rhinitis. Careful questioning showed that the onset of the symptoms coincided with the date of her son's sailing overseas with the Army, and the discussion precipitated hysterical weeping and an episode of hyperesthetic rhinitis. The patient was not accepted as suitable for Anthallan administration, as it was felt that the symptoms were entirely psychic in origin. However, 150 capsules of Anthallan were administered in 21 days without any effect whatever either good or bad.

A second case was a telephone operator 32 years old who complained of the symptoms and had the typical signs of non-seasonal hyperesthetic rhinitis for a period of 3 months. No sign of infection was found in the upper respiratory tract. Anthallan was administered for 3 weeks, a total of 168 capsules, without relief. At this time the patient mentioned that she was having some pelvic pain without any menstrual disturbance. Gynecological examination revealed an ovarian cyst measuring 8 cm. in diameter. The cyst was removed, and all nasal symptoms were relieved at once.

The third case was the sixth of the inconclusive cases listed above. Through an error, Anthallan treatment was begun before roentgenogram and nasal smear reports were made. The administration of Anthallan for 1 week had no effect on the nasal symptoms, which had been present for 10 years. After bilateral purulent maxillary sinusitis was demonstrated by the roentgenogram and by nasal smear, repeated bilateral lavage of the maxillary sinuses relieved all symptoms in 1 week.

These 3 cases illustrate the type of patient in whom failure has occurred. Patients in whom the signs and symptoms of hyperesthetic rhinitis are due to infection, to psychic disturbances, or to ovarian dysfunction will not respond to the administration of Anthallan.

Summary

A study of the therapeutic usefulness and safety of the drug Anthallan was conducted in 42 cases of seasonal and non-seasonal hyperesthetic rhinitis. When Anthallan treatment was started, all patients had suffered from their disease continuously for periods of time averaging 506 days and varying between 11 days and 5 years. These patients had shown relief of only short duration in response to the customary methods of treatment given to the patients before they were treated with Anthallan. In 40 out of 44 courses (90 per cent) of treatment with

Anthallan a beneficial influence of the drug was observed. The improvement varied between 25 per cent and 100 per cent subjectively and objectively, as evaluated by a rigid schedule of numerical ratings of all the subjective and objective manifestations involved. The persistence of the improvement recorded at completion of Anthallan treatment was observed over an average post-observation period of 50 days (minimum 7 days, maximum 248 days). Laboratory studies and clinical examinations did not indicate any harmful effect produced by the treatment with Anthallan.

Conclusions

The results of this study show that Anthallan, when used in doses of 3 to 12 capsules daily over a period of 7 to 35 days by patients selected according to the diagnostic criteria suggested in this study, is a useful drug for obtaining relief in a high percentage of cases of seasonal and non-seasonal hyperesthetic rhinitis, and that Anthallan can be used with complete safety.

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